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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,179	07/11/2003	Bernard F. Erlanger	64081/JPW/AJM/MVM	4371

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,179	ERLANGER ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6,7,12,19-36,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,13-18,37, and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 27 December 2005. Claims 1-5, 8-11, 13-18, 37, and 38 are under final rejection.

Response to Amendment

The rejection of claims 1-5, 13-15, 17, and 18 under 35 U.S.C. §102(b) as being anticipated by Stein *et al.* (1999) **is withdrawn** in view of the amendment.

The rejection of claims 1-5, 8-11, 13-18, and 37 under 35 U.S.C. §102(e) as being anticipated by Frankel *et al.* (US 6,316,03) **is withdrawn** in view of the amendment.

The rejection of claims 1-5, 8-11, 13-16, 37, and 38 under 35 U.S.C. §102(e) as being anticipated by Rothbard *et al.* (US 6,306,993) **is withdrawn** in view of the amendment.

The rejection of claims 1-5, 8-11, 13-18, 37, and 38 under 35 U.S.C. §103 (as) as being obvious over Futaki *et al.* (February, 2001) in view of Awwad *et al.* (1994) **is withdrawn** in view of the amendment.

New Grounds of Rejection Necessitated by the Amendment

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 1-3, 10, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Awwad *et al.* (1994).

Claims 1-3, 10, 17, and 18 are directed to a composition of matter comprising an antibody and a peptide moiety, wherein the peptide moiety comprises an amino acid residue having a nitrogen-containing side chain and wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Awwad *et al.* teach the periodate oxidation of a monoclonal antibody and subsequent conjugation to a peptide linker containing lysine. See Abstract and Materials and methods, Modification of mAb. Awwad *et al.* point out that carbohydrates are covalently bound primarily to the Fc (CH2 domain) of antibodies. See page 23, last paragraph, the second sentence.

Thus, the instant invention is anticipated by Awwad *et al.*

Claim Rejections - 35 USC § 103

Claims 1-5, 10, 11, and 13-18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Awwad *et al.* in view of Futaki *et al.* (2001).

The instant invention is further limited to a composition comprising an antibody covalently bound to a poly-L-arginine peptide of various lengths.

The relevance of Awwad *et al.* is stated above. Awwad *et al.* do not teach the poly-L-arginine peptide.

However, Futaki *et al.* teach the delivery of exogenous proteins into cells by covalently binding arginine-rich peptides to the protein. Futaki *et al.* specifiically teach

the translocation activity of arginine-rich peptides of 8-27 residues and polyarginine peptides of 4-16 residues. See page 5837, Figure 1. Futaki *et al.* further point out that eight residues, or an "octa-peptide" as recited in claim 11, would be an optimal number for efficient translocation, see Abstract.

It would have been obvious to one of ordinary skill in the art at the time the inventions was made to modify the lysine peptide moiety of Awwad *et al.* to the poly-arginine peptide as suggested by Futaki *et al.* with a reasonable expectation of success since an antibody is an exogenous protein and arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The motivation to do so is provided by Futaki *et al.*, who teach the efficient translocation activity of various arginine-rich peptides and disclose that the arginine-based peptides seem to have great cell membrane penetration ability, which would be advantageous for intracellular protein delivery (see last paragraph). Thus, the claimed invention as a whole is *prima facie* obvious over Awwad *et al.* in view of Futaki *et al.*

Claims 1-5, 8-11, 13-18, and 37 are rejected under 35 U.S.C. §103(a) as being unpatentable over Awwad *et al.*, in view of Frankel *et al.* (US 6,316,003).

These claims are drawn to the above-mentioned composition with further limitations of molecular weight, 13 kD, within the range between 11 kD and 16 kD, and of being combined with a pharmaceutically acceptable carrier in a pharmaceutical composition.

The relevance of Awwad *et al.* is set forth above. Awwad *et al.* do not teach these further limitations.

However, Frankel *et al.* teach the use of transport peptides to deliver cargo molecules (see the entire document), particularly, an antibody (see columns 115 and 116, claims 1 and 6). The reference discloses transport peptides such as portions of HIV Tat protein (see column 3, lines 21-31, and SEQ ID NO's: 1-7, for example). The reference also teaches pharmaceutical, prophylactic and diagnostic compositions comprising transport polypeptide-cargo conjugates (see column 3, lines 13-20; column 10, lines 66-67; column 11, lines 1-19).

It would have been obvious to one of ordinary skill in the art at the time the inventions was made to modify the lysine peptide moiety of Awwad *et al.* to the poly-arginine peptide as suggested by Frankel *et al.* with a reasonable expectation of success since arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The motivation to combine is provided when Frankel *et al.* teach the targeting specificity of these peptides for delivering an antibody into the cell nucleus (col. 12, lines 11-15). Thus, the claimed invention as a whole is *prima facie* obvious over Awwad *et al.* in view of Frankel *et al.*.

Claims 1-5, 8-11, 13-18, 37, and 38 are rejected under 35 U.S.C. §103(a) as being unpatentable over Awwad *et al.*, in view of Rothbard *et al.* (US 6,306,993).

These claims are drawn to the above-mentioned composition combined with a pharmaceutically acceptable carrier in a pharmaceutical composition in a kit.

The relevance of Awwad *et al.* is set forth above. Awwad *et al.* do not teach the arginine peptide moiety and the combination with a pharmaceutically acceptable carrier in a pharmaceutical composition.

However, Rothbard *et al.* teach compositions of transport-enhancing polymers containing guanidino side chains (see abstract, particularly, column 2, lines 45-67), specifically, poly-arginine polypeptides (column 3, lines 16-25), covalently attached to a biologically active agent for enhanced transport (see abstract and columns 9-10), which reads on the limitations of claims 1-5 and 37. The reference further discloses sequences of transport peptides consisting of 4, 5, 6, 7, 8, 9, 15, 20, 25 and 30 L-arginine polymers, and a mixture of longer L-arginine polymers of up to 100 amino acids, with an average molecular weight of 12,000 Daltons (column 12, lines 1-9; columns 31-34), which reads on the different molecular weights and peptide lengths as recited in claims 8-11, and 13-16. Finally, the reference discloses that the composition may additionally be packaged with instructions for using it (column 4, lines 36-38), which reads on "a kit comprising the composition of claim 1 and instructions for use" as recited in claim 38.

It would have been obvious to one of ordinary skill in the art at the time the inventions was made to replace the lysine peptide moiety of Awwad *et al.* to the poly-arginine peptide as suggested by Rothbard *et al.* with a reasonable expectation of success since arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The motivation to do so is provided by Rothbard *et al.*, who teach that the use of naturally occurring L-amino acid residues in the transport

polymers has the advantage that breakdown products should be relatively non-toxic to the cell or organism (column 8, lines 26-34). Thus, the claimed invention as a whole is *prima facie* obvious over Awwad *et al.* in view of Rothbard *et al.*

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Louise Humphrey, Ph.D.
10 February 2006

JEFFREY STUCKER
PRIMARY EXAMINER